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Gender differences in otolaryngology: an overview

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Summary. Gender difference in otolaryngology (ENT, Ear Nose and Throat) is a poorly-investigated subject in literature, with the exception of purely epidemiological diversities in oncology. Studies often report sex differences without researching their causes. Sex disparities drastically affect diagnostic and therapeutic procedures in some medical settings as demonstrated by the increasing number of studies published on this subject. Therefore, the aim of this review is to search out data already published about gender differences in ENT, if present, with special attention to their consequences in this discipline. Basically, there are no specific studies about it in the literature. However, there are also significant sex differences in ENT, in terms of epidemiology, anatomy, audiology, inflammation, infectious diseases, pain and cancer susceptibility, in particular for the HPV-related forms. The reasons behind this are to be found in bad habits as smoking or alcohol abuse, more common in men, but also in other, less investigated aspects. This review is directed at improving otolaryngologists' awareness of the existence of gender differences in this medical specialty, as well as the consequences in multiple fields, mostly poorly understood. Studies in the literature also seem to suggest sex differences in ENT diseases, but specific research projects do not exist. Moreover, statistically significant differences in this ambit are often not developed to a profound level. Conversely, more recent works, such as HPV-focused studies, demonstrate that if correctly planned, studies reveal existing gender differences in ENT, especially in prognosis and therapy response.

Key words: gender differences in otolaryngology, head and neck gender differences, sexual differences in otolaryngology, epidemiology in otolaryngology, influence of sex in ENT diseases.

Overview sulle differenze di genere in otorinolaringoiatria

Riassunto. La differenza di genere in otorinolaringoiatria (ORL) è argomento poco indagato in letteratura, fatta eccezione per le diversità prettamente epidemiologiche che emergono soprattutto in oncologia. Gli studi in merito, tuttavia, spesso si limitano a riportare tali dati senza analizzarne il substrato. Obiettivo di questa ricerca, perciò, è stato individuare eventuali lavori pubblicati sulla differenza di genere in ORL e vedere se, effettivamente, quest'ultima comporti delle conseguenze anche in otorinolaringoiatria, attraverso una revisione della letteratura. Si è evinto che, essenzialmente, non esistono lavori specifici in merito. Tuttavia, si apprezzano differenze di genere significative in termini di epidemiologia (ad esempio, nel maschio sono più frequenti lesioni laringee, angiofibroma giovanile, ipoacusia; nella donna atresia coanale e tumori delle ghiandole salivari); anatomia del distretto testa-collo (struttura della coclea), audiologia (acufene, esposizione al rumore), patologia flogistica (acuta, come gli ascessi peritonsillari; cronica, specie in ambito rinosinusitico), dolore (chirurgico, oncologico, diversa risposta alla terapia), suscettibilità al cancro, in particolare HPV-correlato. In ciò, non sono coinvolti solo i fattori associati tradizionalmente alle abitudini voluttuarie quali fumo o alcol, prevalenti nel maschio, ma anche altri aspetti, poco indagati. I dati più interessanti riguardano, certamente, i tumori HPV-correlati. Come per le altre discipline mediche, sarebbe opportuno sensibilizzare l'otorinolaringoiatra, sia dal punto di vista scientifico che pratico, sull'esistenza della differenza di genere in ambiti molteplici, e di cui ancora poco si sa. I lavori riportati in letteratura sembrano suggerire delle diversità in questi termini, anche se studi specifici in merito non esistono e, spesso, una differenza statisticamente significativa non viene indagata ulteriormente. Al contrario, lavori più recenti, come quelli su HPV, mostrano che, se analizzate con una corretta pianificazione dello studio a priori, le differenze di genere esistono e hanno ripercussioni notevoli prognostiche e terapeutiche. Pertanto, anche in ORL andrebbe compreso che le differenze tra sessi non si limitano a una semplice discrepanza epidemiologica, bensì a due tipi distinti di pazienti che potrebbero richiedere un trattamento o avere un'evoluzione clinica differenti.

Parole chiave: differenze di genere in otorinolaringoiatria, differenze di genere nel distretto testa-collo, differenze legate al sesso in otorinolaringoiatria, epidemiologia in otorinolaringoiatria, influenza del sesso nelle malattie ORL.

Introduction

Among ENT diseases, both malign and benign, there are established disparities between men and women in terms of epidemiology. Generally, some conditions and some districts involve one sex more than the other.

For example, laryngeal diseases are more frequent in men. This is true for benign pathology (i.e. vocal cord polyps, cavernous hemangioma, rhabdomyoma, lipo-

ma, pleomorphic adenoma, paraganglioma, hamartoma), as well as for laryngeal cancer (with a mean male: female ratio of 6:1)[1].

Concerning the sinonasal district, there is also a significant male prevalence in most diseases. The most striking case is represented by juvenile nasopharyngeal angiofibroma, which exclusively affects men between 10 and 25 years old[2]. In these patients, there is a confirmed hormonal imbalance between testosterone and estrogens[2]. This tumor might have estrogens receptors liable to increase its growth, even though most of these lesions do not express them[2].

Furthermore, nasal bone fractures are more frequent in males (with a male:female ratio of 2:1) both in childhood and in adulthood, consistent with traumas of other body parts[1].

Some diseases have a differentiated sex prevalence up to a certain age, as with some cardiopathies. Epistaxis, for example, is more widespread among men under 50 years old[1]. After this age, the prevalence is the same as for women[1]. A further example relates to the high-airways diseases, much more common in boys than girls in pediatric age.

Comorbidities can determine a gender difference too. This is the case of nasal polyps, showing a male prevalence among asthmatic patients, but with a similar spread between the sexes in the non-asthmatic population[1].

Inverted papilloma is a sinonasal benign tumor that has a huge male predominance (with a male: female ratio of 2-9:1)[1]. Generally, sinonasal and nasopharyngeal both malignant and benign tumors are rare among women[1]. The same applies to oral and oro-hypopharyngeal cancer[1]. Conversely, benign tumors of the salivary glands, especially pleomorphic adenoma, are more common in the female population[1].

Autoimmune diseases, such as Sjögren syndrome (female:male ratio of 14-24:1), which particularly concerns the head and neck district, are more common among women, as well as in the other sites of the body[1].

In terms of audiological findings, sudden hearing loss behaves differently according to age, being more frequent among men in the IV and V decade of life and among women in the VI decade. Considered as a whole, presbycusis and hearing loss linked to techno and ludopathy are prevalent in men. On the other hand, tinnitus is more widespread in women regardless of age[1].

Finally, some congenital malformations, such as choanal atresia, prevail in women, with a female:male ratio of 5:1 in Caucasian people. Other malformations, such as thyroglossal duct cysts, have no sex predominance. This is also true for other conditions such as facial neuroma, granulomatosis associated with polyangitis or fibro dysplasia.

The influence of sex on the incidence and the features of different conditions has been proven in several medical fields, implying a need for differentiated health care resources and treatments for men and women. Though epidemiological differences between the sexes represent consolidated data, little is known about other aspects of gender disparities in otorhinolaryngology.

Therefore, our analysis of the literature focuses on the most interesting considerations that have emerged in some remarkable ENT conditions in terms of gender difference.

Anatomy and physiology

Anatomical and physiological differences between men and women are more evident in body regions away from the head and neck. As the rule of hormones is less important in this district, we might be led to think that there are no particular differences between gender in this site, but some studies in the literature demonstrate the opposite.

For example, Stuck et al. analyzed chemosensory event-related potentials in 95 people, demonstrating that response to chemosensory stimuli is related to gender. In particular, while suprathreshold measures of olfactory function did not exhibit significant differences ($p > 0.07$), female subjects scored significantly higher in a localization task ($p = 0.014$), indicating that trigeminal sensivity was higher in women than in men[3].

Concerning otology, there are some interesting studies in literature, mainly regarding analyses conducted on animals. Reimann et al., for example, reported some endearing results obtained by physiological studies on gerbils. A gender prevalence in hearing loss, with males being more susceptible, is an established datum. Previous studies demonstrated how cochlear vascularization has a myogenic auto-regulation, based on the involuntary muscle-cells of the spiral modiolar artery. The study of Reimann et al. explained how this mechanism has a different evolution during life in male versus female gerbils. In particular, the spiral modiolar artery, which supplies the cochlear nerve, provides a bed of arterioles showing a different tone in male than in female gerbils during aging[4]. The authors suggested that this mechanism could be one of the reasons for the difference in hearing loss between the two sexes.

Moreover, the advent of more sophisticated imaging techniques, such as high-resolution computed tomography, led to a finer evaluation of the anatomy of some districts, exploring gender and racial differences. In a study conducted on temporal bone data from 161 patients, Thong et al. showed how basal cochlear length is significantly different between genders ($p = 0.0016$)[5].

Voice problems are common in some professional categories, such as teachers. Among these populations, moreover, women emerge as being more damaged[6]. The

reasons behind this depend on anatomical and physiological features that are gender-specific. Laryngeal anatomy, in fact, shows differences between the sexes, both microscopically and macroscopically. Male vocal cords are longer and contain more hyaluronic acid in their lamina propria[7]. The amount of elastin differs too[7]. These considerations might explain why male vocal folds are thicker: the extra hydration of vocal cords due to the hyaluronic acid make them larger[7]. Moreover, female fundamental frequency of vibration is twice that of the male[7]. In the adult population, for example, female vocal folds vibrate at 175-245 Hz on average, while they have a fundamental frequency of about 105-160 Hz among men; considering that vocal folds have about one million vibrations per day during work[8], it is clear that women will exhibit doubled glottic traumatism and, consequently, more voice problems. Women also make greater use of the voice in the non-work context. Vocal nodules are found mostly among women because the higher frequency of vibration leads to more collisions[7]. The lower quantity of hyaluronic acid in female folds also makes them weaker and unable to adsorb shock by gel formation[7]. Hormones also have an important role, both during the development of voice and in its possible change in adult life, with regard to different effects in the two sexes. Androgens, for example, are fundamental during puberty for a complete formation of the male larynx that is impossible if they are lacking. This becomes clear if we consider the example of the "castrati" singers that were particularly valued during the XVIII century. These male singers were castrated before puberty, developing a female larynx that, associated to a male-type pulmonary bellows and sounding board, created a truly singular voice effect. Androgens have irreversible consequences on vocal folds if administered to women. On the other hand, progestins and estrogens have a weak effect on the voice during pregnancy, in pre-puberty age and if taken with contraceptive intent. Voice disorders can appear also in subclinical hormonal imbalances, as in the mixedema of vocal folds linked to hypothyroidsm.

Benign conditions

Some ENT diseases show different behavior in men and women. The reasons are mostly unclear. In this review, we will discuss some common conditions such as chronic rhinosinusitis and peritonsillar abscesses or the different audiological findings that are reported in male and female subjects.

Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) can be divided into two main groups, with or without nasal polyps (respectively CRSwNP or CRSsNP). It is one of most prevalent chronic diseases worldwide, affecting one in seven American adults[9], with a prevalence of around 10.9% in Europe[9]. There are no specific studies relating to gender differences. However, sex disparities seem to exist, as demonstrated by Chaaban et al., and they could be related to the specific type of rhinosinusitis. Their review of the literature seems to suggest that chronic rhinosinusitis with nasal polyps is more frequent in men[9]. But if we consider a cohort of aspirin-sensitive people (a condition strictly related to chronic rhinosinusitis with nasal polyps), polypoid rhinosinusitis is more common in women, with a male:female ratio of 2:3[9]. The reasons for this are not further investigated.

A review, published by Beule et al. in 2015, analytically describes the epidemiology of chronic rhinosinusitis in Europe and reveals some interesting data[10]. For example, considering rhinosinusitis, they show how there is a basal bias, due to the fact that women are more aware of this condition and, consequently, more often seek medical assistance to resolve it[10]. This phenomenon is considered to compensate an actual higher rate of CRS in men, based on more widespread smoking among males (the prevalence of male smokers being 29% for higher and 47.4% for lower social classes, versus 25% and 30.1%, respectively, for women)[10]. Beule confirms that CRSwNP is more common in men, with an incidence of 0.86 for males versus 0.36 for females per thousand and year[10]. The incidence increases with age (respectively 1.68 for men and 0.82 for women per thousand and year), maintaining about the same ratio between the sexes[10].

Considering CRSwNP and CRSsNP together, the majority of the studies report a slight female prevalence[10]. This data is not confirmed worldwide: for example, the male gender is considered a risk factor for CRS in Korea[10]. Beule suggests that one of the possible causes behind this difference could be the longer duration of CRS in men[10]. Moreover, boys have a poorer prognosis after surgical therapy for CRS in pediatric age and this might be a further reason[10]. Conversely, according to other authors, as Klossek et al. in France, the duration of CRSwNP does not show significant differences in the two sexes[10].

There are some conditions associated to CRS, such as asthma or aspirin exacerbated respiratory disease (AERD), in particular in the polypoid form. Women with CRSwNP develop bronchial asthma 1.6 times more often, with a female predominance following the same ratio as that for the asthmatic population[10]. AERD patients are also mostly female (57-76%, according to different authors) and females are also related to an earlier onset and a more aggressive course of the rhinosinusitis[10]. Female predominance also exists in patients suffering from CRS as part of eosinophil granulomatosis with polyangitis[10].

Peritonsillar abscesses

There are some important hints in term of epidemiology, clinical history and microbiology of peritonsillar abscesses (PTA). A retrospective study, conducted by Mazur et al. in 2015 on 111 patients affected by PTA, shows a significant male non-smoking-related predominance (57.7% versus 42.3% for women), as reported by other studies, though the literature also includes reports of an equal male to female ratio[11].

Particularly interesting is a study conducted by Klug in 2014 on 1620 patients from 2001 to 2006 which is almost the only research addressing gender difference in PTA from the beginning as one of the aims[12]. It draws some unexpected conclusions, demonstrating that, if sought, sex disparities can be found and imply significant consequences for patients. The incidence of PTA increases with age, with a peak during the teenage years[12]. There is a female predominance up to the age of 14; in later years males always prevail[12]. Mean annual incidence for girls is significantly higher than that for boys aged 13-14 years (93.4 versus 38.0 cases/100.000 per year, $p = 0.001$)[12]. On the other hand, men were more frequently affected than women in age classes 20-29 and 40-49 years (respectively with $p < 0.001$ and $p = 0.04$)[12].

PTA is a complication of tonsillitis. As we stated in the case of rhinosinusitis, female subjects seem to be more aware of this medical condition. Consequently, Klug suggests that is possible that female patients consult the general practitioner earlier than men, avoiding such complications as PTA thanks to correct treatment for tonsillitis[12].

This data relates to the global incidence of PTA. Stratifying patients by causative agents, they established a female prevalence for all ages in Streptococcus group A, with the exception of girls in the 0-9 age group[12]. There are no gender disparities for the other causative bacteria analyzed[12]. The reasons behind this consideration are not clear[12].

Audiology

The study of Warner-Czyz et al. is one of the best conducted and one of the few in terms of analysis of gender differences in all ENT panorama[13]. It focuses on a population of 96 normal-hearing teenagers to study their attitude to noise. Among adults, it is established that gender biases not only the exposure to high-risk events for noise, but also the presence of high-frequency hearing loss. Moreover, several studies in literature report that the majority of children and adolescents (more than 80%) have at least one high-risk noise behavior. According to Warner-Czyz, boys more often attend high-noise events, at least twice as much as girls (such as sporting events, farm equipment, lawn mowing, hunting or use of firearms)[13]. In terms of engagement in high-risk activities, only playing an instrument is equivalent between genders[13]. Among teenagers, moreover, both boys and girls use musical devices, but boys more frequently and at a significantly higher volume[13].

As observed for the clinical conditions discussed above, females are more sensitive than males to hearing-loss and risky high-noise situations, also in the adolescent population[13]. They consider acoustic high-risk situations more dangerous and are more prone to using anti-noise devices (four times more than boys)[13]. Warner-Czyz et al., finally, suggest that gender influences hearing-risk behaviors regardless of age up to 20 years[13].

Recently researchers started to broaden their attention to include the elderly. In fact, an increasing number of studies demonstrate a significant correlation between hearing loss and cognitive decline[14]. The preservation of intact visual and auditive functions is crucial for a cognitive maintenance[14]. This is true for both sexes, despite the greatest prevalence of hearing loss in the male population, especially for older people. Hearing rehabilitation in elderly subjects, in fact, has been demonstrated to lead to further benefits, beyond restoring the hearing, such as maintaining cognitive function and reducing the risk of depression[14].

Incidence of sudden sensorineural hearing loss seems to increase in advanced age, occurring in particular during cold seasons and among the elderly and women[15]. According to Kim et al., women seem more affected, with a male to female ratio of 1:1.35[15]. Other studies report slightly different ratios, but the reasons behind this are unclear. More women are diagnosed before the age of 70 years, while there is a male predominance after 80 years[15].

Another interesting area is hearing loss due to the chronic use of analgesics. This pharmacological class includes use of 100 mg per day of aspirin, one of the commonest prescriptions worldwide. In two different studies, conducted on two large cohorts of men and women with regular use of analgesics (aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen), followed for almost 20 years, Curhan et al. and Lin et al. revealed some interesting considerations[16,17].

The pathogenesis of analgesic-induced hearing loss is different considering each class of drugs. High doses of salicylates, for example, can imply transient hearing loss and tinnitus[16,17]. On the other hand, low-dose aspirin is an established protection against aminoglycoside and noise-induced hearing loss[16,17]. High-dose NSAIDs are confirmed as ototoxic in animal and human studies, probably thanks to a reduced cochlear blood flow[16,17]. Acetaminophen, finally, may reduce glutathione in the cochlea as in other body sites, reducing the ability of the inner ear to resist oxygen-radicals-induced damage[16,17].

In the analysis on the male population, Curhan et al. found a correlation between chronic analgesic use

and an increased risk of hearing loss, the latter increasing with duration of NSAIDs and acetaminophen use, but not use of aspirin[16]. Moreover, regular assumption of multiple analgesics seems to have an additive effect on hearing loss[16]. Conversely, daily use of 100 mg aspirin was not associated with significant neurosensory auditive damage[16].

The same conclusions were drawn from the large cohort of 62,261 women, analyzed by the same group[17].

Some syndromic forms of childhood deafness, but also some autosomal dominant forms, reveal a male prevalence. The male to female ratio for Goldenhar syndrome, for example, is 3:2 at least[18]. Bilateral sensorineural hearing loss, moreover, occurs in 55% of males and 40% of females affected by Alport syndrome, appearing later and in a milder or even subclinical form in women patients[18].

Speech and language disorders, but especially stammering, are more frequent and associated with poorer prognosis among baby boys, in whom it is more likely to persist[19]. The boys to girls ratio is nearly 3:1[19]. The prognosis is even worse for stammering if the father or first-second degree relatives are affected too[19].

Ménière's disease is a condition characterized by sensorineural hearing loss, tinnitus and vertigo. It is often associated with migraine or autoimmune disorders. It can be divided into 5 subgroups having different patterns of signs and symptoms, according to Frejo et al.[20] a) group 1, most frequent (46%), with metachronic hearing loss and without migraine or autoimmune disease; b) group 2, with synchronic hearing loss and without migraine or autoimmune disease; c) group 3, familial; d) group 4, associated to migraine; e) group 5 (representing 11% of cases), associated to auto-immune disease. Women are more affected, especially in the last group.

Pain perception

Pain treatment concerns ENT practice in nearly all fields, including inflammatory disease, cancer and post-surgical management. Nevertheless, it is a truly scarcely-discussed argument in literature. Furthermore, pain perception seems to be different in men and women and this consideration cannot be ignored by the otolaryngologist in everyday patient support.

Gender-based differences in pain are reported, in particular following surgery or in other acute conditions, where women declare higher levels[21]. Women complain about aches especially during the day, while men do so in the evening[21]. Moreover, females describe pain as being more intense than males; on the other hand, men hurt after surgery for a longer period than women[21]. The reasons behind these disparities remain unclear[21].

It is difficult to quantify pain in oncological patients, because it is due to numerous factors including the stage of the disease, the primary site of the tumor, the type of treatment, psychological implications.

Somatic pain, such as the pain that follows bony metastases, is more common in men, while women are more affected by visceral discomfort[21]. Neuropathic pain has the same incidence in both sexes[21].

Despite this scenario, women often receive fewer analgesics than men both in post-surgical and cancer pain[21]. In particular, males obtain a significantly greater quantity of opioids ($p < 0.001$)[21].

It is important to consider that female response to opioids differs from the male response[21]. The biological background of this event is at least partially explained in animal models by CYP-4503A cytochrome, responsible for fentanyl, midazolam and methadone metabolism[21]. It has been demonstrated that endogenous sex steroid hormones can influence the expression of the CYP-450-3A cytochrome isoforms and, consequently, the different metabolism of midazolam and alfentanyl which increased from 20% to 40% in women compared to men[21]. Though animal models do not always correspond to the human, these considerations have serious clinical and therapeutic implications.

Regarding equal administration of morphine, there are no significant differences by surgical site[21]. An exception, on the contrary, is found in oral surgery where men consume 2.4 times more opioids than women[21]. In this case, females obtain more effective analgesia than men (the opposite of what emerges from some animal studies)[21].

Finally, women are more exposed to side-effects such as opioid-induced nausea or vomiting: this is one of the reasons why they present greater pain-related disability[21].

Cancer

Males are generally more prone to developing cancer, especially for the hematologic forms[22]. During childhood, prognosis is worse in boys and this consideration is valid for adult men too, showing worse overall survival and higher mortality rates than women[22]. Secondary tumors, moreover, are more frequent in men who survived cancer[22].

In the United States, the global incidence of cancer is 553.0 for males and 416.5 for females per 100,000 people per year, with mortality rates higher for men (male: female ratio = 1.46)[22].

In a study published in 2012, the IARC agency describes the universal nature of gender disparities in cancer, finding a male prevalence in 32 of 35 body sites analyzed ($p<0.0001$)[22]. Moreover, they show how males have higher incidence rates of cancer globally, regardless of the geographic region considered[22].

One of their remarks is of particular interest to the otolaryngologist: the highest disparity between the sexes has been found in laryngeal and hypo pharyngeal cancer, with a six-fold preponderance for males[22]. It is interesting to note that lip cancer is the fourth-classified cancer in the male-to-female ratio[22]. Furthermore, when stratifying people by age, a male predominance also prevails in salivary gland tumors in older people[22].

Several factors are involved in the gender difference in the development of cancer. Environment surely has a greater role than for other types of diseases. In parallel sex hormones, epigenetics and bio-molecular mechanisms such as microchimerism and autophagy are present. The main cause of male excess in cancer incidence seems ultimately due to environmental and professional exposure, including smoking, diet, sunlight[22].

Considering the previous study, male-to-female differences in cancer seem to be a matter of epidemiology. The underlying reasons, on the contrary, could be more complicated. In ENT panorama, prognostic role of sex has been studied up to the present in Human Papilloma Virus (HPV) related cancers.

HPV is a prognostic marker for oropharyngeal squamous cell carcinoma (OPSCC). Gender and ethnic differences in prognosis are not well established yet, because studies conducted in this scope are poor in female and non-white subjects. This is a mirror of demographic features of this type of cancer. Sex-related differences in OPSCC are poorly investigated, even though recent multi variate analysis confirms that men have a worse overall survival rate (OS). HPV-positive OPSCCs are more likely to be white and young and have better survival prospects both on primary diagnosis and upon recurrence than HPV-negative[23].

At present, most studies regarding OPSCC prognosis are based on male and white patients[23]. The incidence of OPSCC is certainly lower among women and non-whites, but the majority of OPSCCs in these subjects are HPV-positive too[23].

Fakhry et al. carried out more profound research into these disparities in a study conducted in 2016 on 860 patients (36.2% women, 63.8% men) affected by oropharyngeal (n = 239), oral (n = 253), laryngeal (n = 243) and nasopharyngeal cancer (n = 125)[23]. They found that the majority of OPSCCs was HPV-positive both for men (58% of cases) and women (52% of cases), though the overall incidence of OPSCC is lower among women[23]. The clinical features of OPSCCS men and women were similar, but women were more likely to be white ($p = 0.005$) and less likely to be tobacco ($p<0.001$) or alcohol users ($p = 0.008$)[23].

This analysis confirmed that both HPV and p16 positivity significantly improve OS at 5 and 10 years[23]. Survival was also better for women with HPV-positive OPSCC (at 5 years 73.1% in women versus 58.3% in men; at 10 years 58.1% versus 39.6%)[23].

In the multivariate analysis, female sex and HPV-positivity were both associated with better survival rates among OPSCCs[23]. In parallel, there was no interaction between HPV and gender ($p = 0.23$), suggesting that HPV status could have a similar prognostic significance for both sexes in OPSCC[23].

On the other hand, in non-OPSCCs (oral cavity, larynx and nasopharynx), HPV does not impact on OS[23]. In the non-OPSCC forms, women have a similar survival rate to men for nasopharyngeal and laryngeal cancer, but a lower survival prospect for tumors of the oral cavity[23]. In multi-variate analysis for non-OPSCC, neither gender nor ethnic influenced OS, whereas older age, high grade, nodal stage and actual alcohol use did[23].

To summarise, it can be affirmed that gender is an important prognostic factor for OPSCC, independently of HPV status[23]. The reasons for this are still unknown. It could be a matter of environmental factors, such as alcohol or tobacco use, or comorbidities, but is also a question of distinct phenotypes of the disease in men versus women, as demonstrated for non-squamous lung cancer[23].

In 2013, Chaturvedi et al. analysed worldwide trends in oral (OC) and oropharyngeal cancers (OPC), comprising 182,736 patients[24]. They found increasing incidence of OPC and a parallel rise in HPV-positive OPCs since 1980, particularly among men[24]. In particular, this was observed in developed countries including Europe, Japan, Australia and North-America[24]. Among women, data suggest increasing incidence rates too, but from 2 to 17 times lower than rates in men[24]. Moreover, significant increases in OPC incidence were reported only in European countries for women[24].

This study also shows an increasing rate for both OC and OPC, against a global reduction of some of the greatest risk factors, including tobacco and alcohol[24], suggesting that a change in sexual behavior, especially in developed countries, could explain this phenomenon in both genders[24].

Conclusions

As can be seen from the discussion above, the study of gender and its implications in otolaryngology is substantially an uncharted field. Specific studies are practically non-existent and the few focused on the argument are often affected by demographic biases.

On the other hand, disparities seem to be present between the sexes not only in terms of incidence and prevalence of diseases, but also in physiopathology, symptoms, treatment and response to therapy. Moreover, trends appear to be undergoing change among these differences.

In this scenario, it is fundamental for the otolaryngologist to comprehend the importance of gender medicine not as a separate branch that does not concern ENT specialty, but as a filter through which everyday practice has to be evaluated.

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Key messages

- Gender difference in otolaryngology is a poorly-investigated subject in literature. Studies often report sex differences without researching their causes.
- There are significant sex differences in otolaryngology, in terms of epidemiology, anatomy, audiology, inflammation, infectious diseases, pain and cancer susceptibility, in particular for the HPV-related forms.
- The reasons behind significant sex differences in otolaryngology are to be found in bad habits as smoking or alcohol abuse, more common in men, but also in other, less investigated aspects.
- Statistically significant differences in otolaryngology are often not developed to a profound level.
- More recent works, such as HPV-focused studies, demonstrate that if correctly planned, studies reveal existing gender differences in otolaryngology, especially in prognosis and therapy response.

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